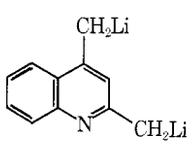
In contrast to the conversion of **4a** to **4b** in THF–hexane, **4a**, prepared from **3** and *n*-butyllithium in ethyl ether–hexane, did *not* isomerize to **4b** even after 96 hr. In fact, the opposite could be realized. Thus, **4b** was prepared from dimethylaminolithium and **3** in THF–hexane and the reaction mixture was divided into two parts. One part was trapped with benzophenone to afford **5b**. The other part was evaporated to dryness and treated with ethyl ether, **3**, and benzophenone to give only **5a**.

It can be concluded from the above that the formation of solvated organometallics **4a** and **4b** is either kinetically or thermodynamically controlled depending on the solvent. Thus, **4a** solvated by THF is the kinetic product while **4a** solvated by ethyl ether is the thermodynamic product. On the other hand, **4b** solvated by THF is the thermodynamic product while **4b** solvated by ethyl ether is the kinetic product. The relative thermodynamic stabilities of solvated **4a** and **4b** can be rationalized on the basis that the less sterically bulky THF interacts less with the peri-hydrogen atom of **4b** than does ethyl ether.

These isomerizations are similar to those obtained with excess alkylbenzenes and alkylsodium and potassium reagents,[2] and to those realized with certain alkali derivatives of benzyldimethylamine,[3] though no solvent effects were reported. The interconversions of **4a** and **4b** probably occur *via* a small amount of unionized **3** but may also involve dianion **4c**; compounds like **4c** have recently been prepared from polymethylpyridines.[4]



4c

In conclusion, synthetically useful side-chain metalations of six-membered polyalkyl nitrogenous aromatic heterocycles can be realized provided that careful attention is directed toward the choice of solvent, metalating agent, metallic cation, and time. Studies on systems other than **3** are currently under investigation in these laboratories.

Supplementary Material Available. Experimental data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2659.

References and Notes

(1) E. M. Kaiser, G. J. Bartling, W. R. Thomas, S. B. Nichols, and D. R. Nash, *J. Org. Chem.*, **38**, 71 (1973).
(2) R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *J. Amer. Chem. Soc.*, **85**, 3984 (1963), and references cited therein.
(3) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).
(4) G. B. Trimitsis, S. G. Benzunas, and R. C. Gorski, Abstracts, 7th Great Lakes Regional Meeting of the American Chemical Society, Kalamazoo, Mich., June 1973.

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A Unique Example of Virtual Proton–Proton Coupling in Purine Nucleosides

Summary: A unique long-range virtual coupling between C-1′ H and C-3′ H of 2′-*O*-benzyl derivatives of adenosine and inosine is reported.

Sir: Our interest in developing techniques for the chemical synthesis of oligoribonucleotides of defined chemical structure has led to the synthesis of a number of ribonucleosides having the 2′- or 3′-hydroxyl function selectively protected by a benzyl[1] or *p*-methoxybenzyl[2] group. It was of interest to study the conformation in solution of certain of these benzyl ribonucleosides, since molecular models suggested that overlap (stacking) of the benzene and heterocyclic moieties could occur in the 2′-*O*-benzyl series but not in the 3′-*O*-benzyl nucleosides (Figure 1). As has been previously shown by a number of groups,[3–5] pmr spectroscopy in aqueous (D_2O) solution affords an excellent method of evaluating a stacking interaction between two or more "heteroaromatic" bases in a molecule.

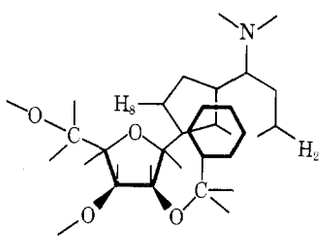

Figure 1

Examination of the pmr spectra of 2′-*O*-benzyladenosine (**1**) and 2′-*O*-benzylinosine (**2**) in D_2O solution (~0.10 *M*) at 60 MHz revealed a striking anomaly in the signal attributable to C-1′ H. β-D-Ribofuranosylpurine spectra normally exhibit $J_{1',2'}$ values of around 6 Hz and the C-1′ H signal appears as a clean doublet. This was indeed the case for **1** and **2** in $(CD_3)_2SO$ solutions. In D_2O, however, the signal due to C-1′ H appeared as a complex multiplet. The spectrum of 2′-*O*-benzyluridine, on the other hand, revealed an entirely normal doublet ($J_{1',2'}$ = 6.0 Hz) attributable to the C-1′ H signal.

As previously observed,[1,2] 2′-*O*-benzyl ribonucleosides in aqueous solution appear to exist in a "folded" conformation (Figure 1) in which the benzene ring is stacked with the heterocyclic moiety. It was, therefore, of interest to determine if an elevated temperature would lead to unstacking and whether this would have an effect on the multiplicity of the C-1′ H signal. Therefore, pmr spectra were recorded of a 0.046 *M* solution of **1** in D_2O at 30° and at 70°. Unstacking at the higher temperatures was confirmed by the downfield shifts of 0.06, 0.13, 0.10, and 0.10 ppm for C-8 H, C-2 H, the phenyl protons, and C-1′ H, respectively. The differential shifts of C-8 H and C-2 H support a conformational model in which the benzene ring is stacked primarily over the pyrimidine ring of the purine. In addition to the deshielding experienced by C-1′ H over this temperature range, the signal collapsed from the multiplet to a clean doublet ($J_{1',2'}$ = 5.5 hz). This observation strongly suggested that the observed multiplicity arose from a conformationally dependent long-range coupling between C-1′ H and another proton in the molecule resulting from stabilization of a specific ribose conformation by an intramolecular stacking interaction. Unstacking at higher temperature presumably permits the establishment of a mobile equilibrium of conformers. Because of the complexity of the spectrum arising from the sugar portion of the molecule

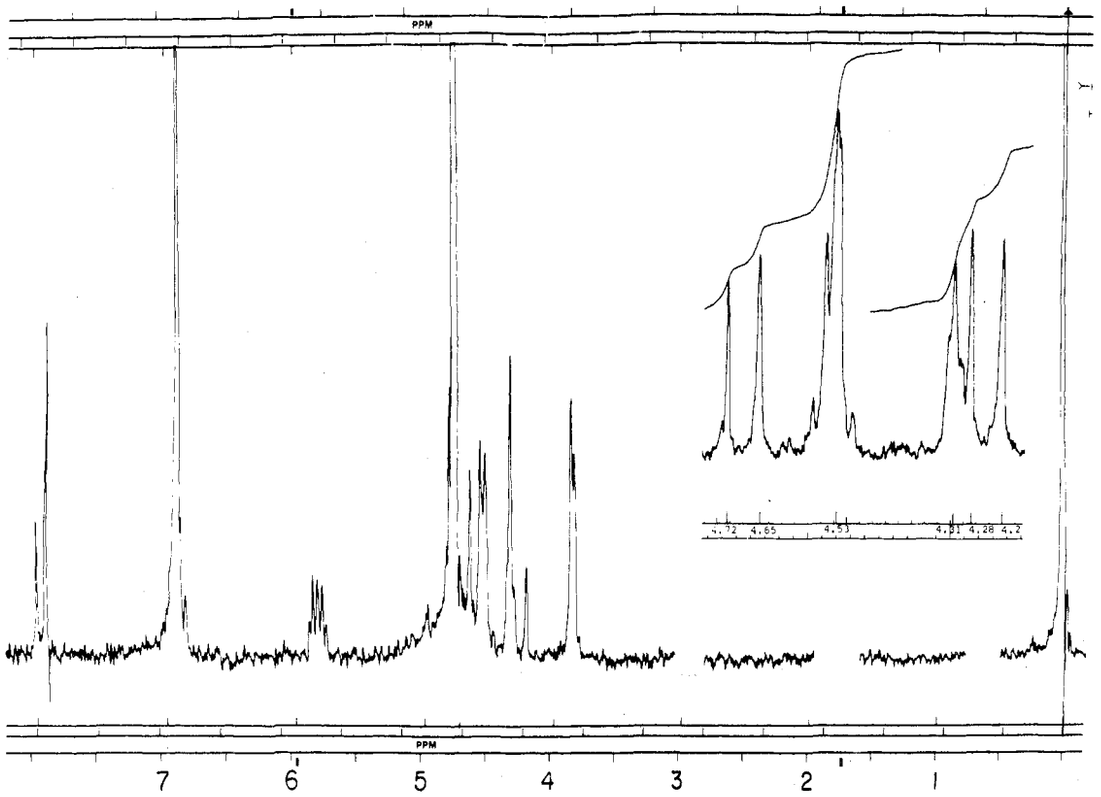

Figure 2. 220 MHz spectrum of 2′-*O*-benzyladenosine (1) in D_2O.

and the benzyl methylene, as well as the presence of a substantial HDO peak in the same region, it initially proved impossible to assign all of the proton signals in spectra obtained at 60 and 100 MHz. The spectrum obtained at 220 MHz (Figure 2) was readily assigned, however, and the possibility of long-range coupling with one of the benzyl methylene protons was eliminated by the identification of the four sharp, well-resolved lines of a typical AB quartet centered at δ 4.47 (J_{HCH} = 12 Hz) for the methylene protons. The anomeric proton signal still appeared as a multiplet; complete assignment of the 220-MHz spectrum revealed that the signals of C-2′ H and C-3′ H were superimposed.

The knowledge obtained from the 220-MHz spectrum enabled the assignment of the superimposed signals arising from C-2′ and C-3′ H at 60 and 100 MHz. Decoupling experiments confirmed that C-1′ H was coupled only to C-2′ H and C-3′ H; irradiation of the signal due to the latter protons caused the collapse of the C-1′ H multiplet to a singlet.

These experiments establish that the unexpected splitting of the anomeric proton signal in **1** and **2** is the result of long-range coupling between C-1′ H and C-3′ H. This could arise either as a result of four-bond coupling or virtual coupling. Four-bond coupling across σ bonds usually requires a planar zigzag conformation of the bonds involved. Examination of molecular models reveal that this criterion is not met in the stacked conformation of 1 and **2.** In order for virtual coupling to occur, three conditions must be met.[6] First, C-2′ H and C-3′ H must be strongly coupled. The dihedral angle between these two protons is small, and according to the Karplus relationship, $J_{2',3'}$ should be large. Only a few such couplings have been determined, but those which have been reported range from 4.5 to 6.5 Hz.[7] The second criterion is that C-1′ H be only weakly coupled to C-3′ H; the usual absence of any measurable coupling in purine nucleosides attests that this condition is met. Finally, the separation between the C-2′ H and C-3′ H signals must be less than $J_{2',3'}$. Careful examination of the 220-MHz spectrum reveals that, even at this high field, only ~1.5 Hz separates the centers of the C-2′ H and C-3′ H signals.

For final confirmation, a partial computer simulation of the 220-MHz spectrum of **1** using the LAOCOON III program was undertaken. The use of $J_{1',2'}$ as 6.5 Hz, $J_{2',3'}$ = 5.0 Hz and the actual chemical shifts of C-1′ H, C-2′ H, C-3′ H, and C-4′ H resulted in a simulated spectrum of the C-1′ H coupling pattern that is in excellent agreement with the measured 220-MHz spectrum.

Based upon these considerations, the unique splitting pattern of the anomeric protons of **1** and **2** have been shown to result from virtual long-range coupling between C-1′ H and C-3′ H. This phenomenon appears from the limited data available to be specific for base type (purine *vs.* pyrimidine) and for aqueous solutions. Solubility limitations in aqueous solutions have prevented similar analysis of 2′-*O*-benzylcytidine and 2′-*O*-benzylguanosine spectra. To our knowledge, this represents the first report of such a phenomenon in a nucleoside.

Studies now in progress are expected to provide more specific information on ribose conformational equilibria in these interesting systems and to reveal the scope of the phenomenon by examination of 2′-*O*-benzyl nucleotides and oligonucleotides.

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References and Notes

(1) L. F. Christensen and A. D. Broom, *J. Org. Chem.*, **37**, 3398 (1972).
(2) A. D. Broom, L. F. Christensen and J. T. Uchic, Abstracts of the 164th

National Meeting of the American Chemical Society, New York, N. Y., 1972, ON 137.
(3) P. O. P. Ts'o, M. P. Schweizer, and D. P. Hollis, *Ann. N.Y. Acad. Sci.*, **158**, 252 (1969).
(4) S. J. Chan and G. P. Kreishman, *J. Amer. Chem. Soc.*, **92**, 1102 (1970).
(5) C. D. Barry, J. A. Glasel, A. C. T. North, R. J. P. Williams, and A. V. Xavier, *Biochim. Biophys. Acta*, **161**, 101 (1972).
(6) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 33–41.
(7) C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.*, **95**, 2333 (1973).

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Synthesis of the Isomers of 3-Butyl-5-methyloctahydroindolizine, a Trail Pheromone of Pharaoh Ant

Summary: The four stereoisomers of 3-methyl-5-butyloctahydroindolizine, a trail pheromone of the Pharaoh ant, have been synthesized by methods that unambiguously defined their stereochemistry.

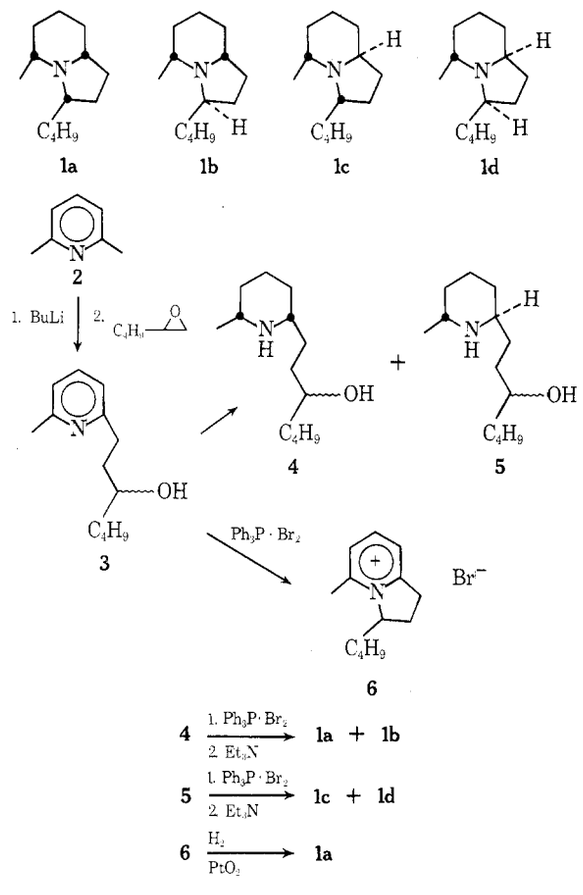
Sir: Ritter, *et al.*,[1] recently described the isolation and identification of a 3-butyl-5-methyloctahydroindolizine as a trail pheromone of the Pharaoh ant, *Monomorium pharaonis* (L.). Which of the four possible geometrical isomers (**1a–d**) of this structure was the active pheromone was not determined. Because of our interest in the synthesis of pheromones of potential utility for pest control,[2] and because the reported[1] synthesis of **1a–d** would not be practical for preparation of the individual isomers, we undertook syntheses of each of the isomers by routes that would define their stereochemistry and allow their isolation. We here report successful preparations of each of the isomers from 2,6-lutidine (**2**) (Scheme I).

Sequential treatment of **2** with *n*-butyllithium and hexene 1-oxide gave the alcohol **3** [bp 92° (0.06 mm), n^{27}D 1.5022].[3] Cyclization of **3** with triphenylphosphine dibromide ($Ph_3P{\cdot}Br_2$) provided the dihydroindolizinium bromide **6** (characterized as the iodide, mp 126–127°) which was hydrogenated over PtO_2 to give the *all-cis*[4]-3,5-dialkyloctahydroindolizine **1a** [bp 119° (27 mm), n^{25}D 1.4669].

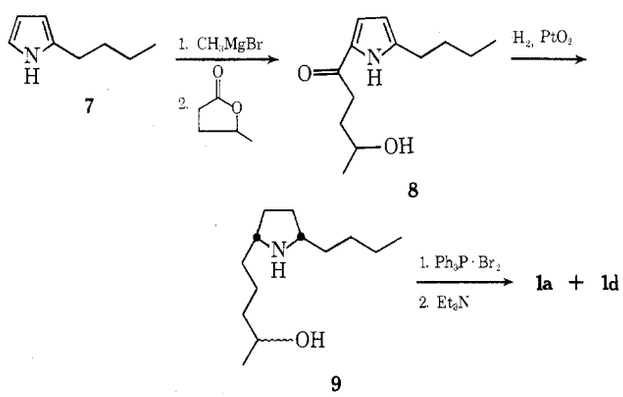
Hydrogenation of **3** gave the *cis*[5]-piperidyl alcohols **4** (mp 55–63°). Cyclization of **4** with $Ph_3P{\cdot}Br_2$ followed by triethylamine gave a mixture (separated by spinning-band distillation) of **1a** and **1b** [bp 125° (27 mm), n^{25}D 1.4704].

The final two isomers, **1c** and **1d,** whose substituents on the piperidine ring bear a trans relationship, were prepared analogously. Reduction of **3** with sodium and ethanol gave an 80:20 mixture of **4** and its trans isomer **5,** respectively. Seeding an acetonitrile solution of the crude mixture with **4** initiated crystallization of that isomer; the mother liquor contained approximately equal parts of **4** and **5.** Spinning band distillation achieved final separation of the *trans*-piperidyl alcohol **5** [bp 77° (0.005 mm), n^{25}D 1.4732]. Cyclization of **5** with $Ph_3P{\cdot}Br_2$ then gave **1c** [bp 121° (27 mm), n^{25}D 1.4699] and **1d** [bp 125° (27 mm), n^{25}D 1.4695]; these were also separated by spinning-band distillation. A variety of packed glc columns (Carbowax 20M, SE-30, others) served to distinguish the indolizidines and to monitor the

Scheme I



Scheme II



distillations. Although **1b** and **1d** could not be separated by gas chromotography, the synthetic routes chosen circumvented the necessity for separation. The production of *cis*-dialkylpiperidines by catalytic hydrogenation of the corresponding pyridines provided the basis for assigning the stereochemistry at positions 6 and 9 of **1a–d;**[6] the stereochemistry at position 3 of **6** (and therefore of **7**) was established by the alternate preparation of **1a** from **6.** To assign the stereochemistry at position 3 of **1c** and **1d,** we again turned to the principle of cis hydrogenation, in this case to produce the cis-2,5-disubstituted pyrrolidine **9** (Scheme II). γ-Valerolactone was added to the Grignard reagent from 2-butylpyrrole (**7**) to give **8** (mp 63–64°). Hydrogenation (PtO_2, 50 psi) of **8** gave the pyrrolidinyl alcohol **9** which was not purified but instead was cyclized directly with $Ph_3{\cdot}Br_2$ to a mixture consisting mainly of **1a** and **1d,** thereby establishing **1d** as the isomer with hydrogens at positions 3 and 9 situated cis to each other. Small amounts of